Individual Susceptibility to NIHL and New Perspective in Treatment of Acute Noise Trauma

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Summary

There would be great interest in finding a test which predicts individual susceptibility to permanent threshold shift. Such test would allow identification of people who are most likely to suffer hearing damage in high noise areas and thereby reduce the number of people presenting NIHL.

Considering the consequences of NIHL for the health of the soldiers, the cost of the treatments, the operational and compensation costs induced by NIHL, it is necessary to assess the actual efficiency of the present medical treatments of the acoustic trauma. Preliminary results indicate that some treatments speed up the recovery and correspond to lower threshold shifts and smaller morphological damages. Moreover, experiments are in progress to assess the interest of new treatments applied directly to the inner ear.

Individual Susceptibility to NIHL

1. Introduction

It has long been agreed that there would be great interest in finding a test which predicts individual susceptibility to permanent threshold shift (PTS). Thirty–five years ago, Ward [1] analyzed about 20 proposed tests of individual susceptibility, and found none of them good enough to be useful. Since that time, many other publications on this subject have appeared. Most of the procedures were described by Howell [2] and Buck and Franke [3].

The proposed tests can be divided into two major groups, nonauditory and auditory.

2. Nonauditory tests

Bonaccorsi [4] showed, in men and guinea pigs, that a correlation exists between the concentration of melanin in the stria vascularis and susceptibility to noise. Because the concentration of melanin in the iris of the eye is positively correlated with the concentration in the stria vascularis, it follows that dark eyes are correlated with low noise susceptibility.

It has also been proposed that there is a correlation between general health condition and susceptibility. Different studies [5,6] indicate that good cardiovascular function (i.e., low blood viscosity, low rate of blood platelets aggregate, low rate of cholesterol…) decreases the risk of hearing loss.

Overall, however, the relationship between nonauditory factors and susceptibility is sufficiently weak that they do not seem to offer a basis for an effective susceptibility test.

3. Auditory tests

There are a very large number of proposed tests, almost all of them using some procedure to determine the sensitivity to temporary threshold shift (TTS).

Carhart [7] proposed the "Threshold of Distorsion Test" as an index of susceptibility to TTS. This test used the level at which pure tone nonlinear combination tones could be heard. The "Threshold of Octave Masking Effect" proposed by Humes et al. [8] is based on a similar principle. The "Loudness Discrimination Index", which is based on recruitment (usually observed after a subject is exposed to intense noise), was proposed as an early indicator for TTS [9]. Pederson [10,11] showed that changes in the cochlea due to intense noise alter the slope of the temporal integration function. Thus, Humes [12] proposed that "Brief Tone Audiometry" might be an indicator of susceptibility. Humes [12] also proposed that "Speech Discrimination in Noise" might be used to detect "fragile" ears because frequency integration in the ear might be affected long before any TTS could be detected.

Some authors tried to establish a correlation between the threshold of audibility and the susceptibility to noise [13]. In normal hearing subjects, thresholds are partly determined by the performance of the transfer function of the outer and the middle ears. Therefore, low thresholds could indicate that a large amount of acoustic energy is transmitted to the inner ear [14]. Measurement of the "Middle-Ear Acoustic Reflex", which modulates the transmission of the acoustic energy to the inner ear, has also been suggested as a test of susceptibility [15]. It has been proposed that reflex latency, rise time and fall time could give an indication of sensitivity to TTS. On another hand, as medial olivocochlear efferents connected to the outer hair cells might protect the cochlea against the damaging effects of intense sound exposure [16, 17], the possibility to assess the interindividual susceptibility from the measurement of the "Inner-Ear Acoustic Reflex(es)" when stimulating the ipsilateral and/or the contralateral ear exists, even if controversial [18].

All the auditory tests purport to predict individual susceptibility to TTS, but not to PTS. In fact, most of the tests deals with TTS in humans, and there is no ethical

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way to induce a PTS in humans for experimental purposes. So the problem for all tests is that there must be a correlation between sensitivity to TTS and sensitivity to PTS if they are to have any practical value.
Temkin [19] in 1933, first stated the hypothesis that there should be some relationship between TTS and PTS. In the intervening years, discussion has gone on and there is still no definite answer as to whether this relationship exists or not. Burns and Robinson [20] measured the PTS acquired during a worker's previous employment and compared it to the TTS acquired during one working day. They reported that the group of workers which showed a lower initial hearing sensitivity developed less TTS at the end of the working day. They also concluded "that a higher susceptibility to TTS tends to be associated with higher susceptibility to occupational hearing loss, and vice versa". However, there is considerable uncertainty with respect to the hearing thresholds before the work experience, which makes it difficult to interpret these findings unequivocally. Using the data of Richartz [21], Kraak [22,23] reported a close relationship between TTS integrated over time (ITTS) and PTS. This approach correlates the growth and the recovery of ITTS for a four hour exposure with the PTS due to about one year exposure to the same noise. Although there are some methodological questions, this method shows a surprisingly good correlation between TTS and PTS. Kryter et al. [24] postulated that the TTS observed after one working day should approximate the amount of PTS after ten years work in the same environment. However, these data are mean data for groups and are not applicable to the prediction of individual susceptibility. Jerger and Carhart [25] exposed subjects to 3 kHz tones at 100 dB for 60 seconds and then measured the time it took threshold at 4.5 kHz to return within 20 and 10 dB of pre-exposure levels. The subjects then took a course on jet-engine maintenance where they were regularly subjected to intense noise exposure. Eight weeks after the exposure, PTS was measured. Their results suggest that subjects with a longer recovery time for TTS are more susceptible to PTS. Although there is a trend in their data, the large scatter shows that recovery time is not highly correlated with susceptibility to PTS. Pfander [26] did a study in which 100 soldiers were exposed to three different types of noise (two white noises and gunshots). The five soldiers who showed the slowest recovery from the gunshot also showed PTS at the end of the shooting training. Therefore, he suggested that the recovery time or TTS might be the factor characterizing susceptibility to noise.
The foregoing tests show some relationship between TTS (or related factors) and PTS. Unfortunately, for the most part they were designed to show the correlation for groups, rather than for individuals. It is possible that a test of susceptibility to PTS based on TTS measures may also work very well for individuals. The literature gives no direct answer to this issue, but rather a lot of inconsistencies. Therefore, some authors [3] decided to evaluate whether it was possible to find some correlation between TTS (or related parameters) and susceptibility to PTS for at least one case.
Because of ethical problems, these experiments were performed on animals (guinea pigs). Animals were exposed to a 1/3 octave band noise of moderate level and TTS of about 25 dB were measured (phase I). One week later (after complete recovery), the same animals were exposed to the same noise at a much higher level. PTS were produced and measured up to 40-60 days post-exposure (Phase II). The essentially low correlation between PTS and TTS at the individual level seem to indicate that there are different mechanisms involved (i.e., maximum TTS appears one octave higher than the noise stimulus, but maximum PTS is measured at the center frequency of the noise, meaning that TTS is induced in a different part of the cochlea than PTS). TTS could be mainly due to metabolic depletion or neurotoxicity (vacuolization at the base of the inner hair cells), PTS could be the result of structural modification or destruction of hair cells. This distinction between the metabolic and the mechanical damages is especially relevant to the weapon noises: acute acoustic trauma and PTS may occur following a single exposure to an impulse (mechanical origin). Then, susceptibility to PTS should be tested using methods which are more directly related to the mechanical origin of the PTS. Unfortunately, this means that any test which is perfectly reversible (i.e., a test inducing a TTS of metabolic origin) might not give enough information about PTS.

4. Discussion

It is also essential to stress that the individual susceptibility to noise is probably not the same as a function of age and health condition of the subjects. Somebody who is rated as resistant to noise could, under unpredictable conditions (having a cold, using medicaments...), become especially susceptible. Therefore, it would be hazardous to rate once and for all the auditory susceptibility of any subject.
Very recently a survey performed by Job et al. [27] on 1208 young recruits showed that the harmful effect of noise exposure (PTS, tinnitus) was strongly dependent on the presence of repeated episodes of otitis media in infancy or childhood (even when no sequelae was observable during the otoscopic examination at the time of the survey). This study indicates that a test for individual susceptibility to NIHL could be looked for in other directions than the usual relationships between TTS and PTS.

Treatment of Acute Noise Trauma

1. Introduction

In some countries (France, Germany...) all soldiers suffering acute acoustic trauma receive a medical treatment at the hospital. In France, for the three years 1993, 1994 and 1995, 1,796 soldiers have been treated in

the ENT departments of the military hospitals (total number of days of hospitalization: 7,974). In 1996, 966 cases of acoustic trauma have been reported and treated at a medical cost of 4 million dollar. In Germany, the cost of those treatments is 2.5 million dollar a year. In other countries (United Kingdom, USA...), the soldiers in the same situation are not treated (they are only withdrawn from hazardous noise exposure). However, the acoustic trauma is responsible for many other expenses:

- in all countries, following an acoustic trauma the soldiers are temporarily retired from active service. Then, if they retain large permanent hearing losses they can be definitively withdrawn from front line service. For specialized personnel large formation and training expenses may be definitively wasted,
- in the past 50 years or so, many acoustic trauma went untreated (the actual efficiency of the treatments is a matter of controversy [28], see below). Therefore, in all countries huge compensations are paid each year to the veterans for hearing loss as a primary disability. In the USA, 291.6 million dollar have been distributed in 1999 to 56,792 veterans [29]. In France, the annual cost of the compensations for Noise-Induced-Hearing-Loss (NIHL) is evaluated to 60 million dollar. In Belgium, about two thirds of the 6 million dollar paid yearly to the veterans for all kinds of disabilities correspond to NIHL. Moreover, the acoustic trauma represents the first cause of morbidity in the military during peace time!

Considering:

- the important consequences of NIHL for the health of the soldiers,
- the cost of the medical treatments of the acoustic trauma (in some countries),
- the huge operational and compensation costs induced by NIHL (in all countries),

it is necessary : (i) to know whether the present medical treatments of the acoustic trauma are relevant and must continue to be prescribed in order to advice, or not, to use similar treatments in the other NATO countries, (ii) to determine the most efficient treatment (if any), (iii) to look for new treatments.

Given the difficulties to assess the actual efficiency of the medical treatments of the acoustic trauma in man (ignorance of the pre-exposure hearing condition, ignorance of the noise exposure parameters, use of different treatments, various implementation delays of those treatments, difficulties to differentiate between the normal physiological recovery and the medical assisted recovery, impossibility to perform morphological observations of the sensory organ, ethical problems prohibiting the use of control groups...), the best approach is to use animal experimentation. Animal experimentation allows to study on a statistical basis the functional and the morphological aspects of hearing recovery (and hence the efficiency of such or such treatment) on treated and on untreated groups of animals (controls).

2. Hearing damage from noise

Intense sound stimulation results in various structural changes leading to functional auditory impairment. It is well known that intense sound exposure induces two major types of damage : (i) injuries occurring first in the first row of outer hair cells (OHC), then in the inner hair cells (IHC), and subsequently in the second and third rows of OHC [30], and (ii) massive destruction of the dendrites of the primary auditory neurons below the IHC [31,32,33]. It has been demonstrated that after acoustic trauma, the acute hearing losses are due both to hair cell injuries and to dendrite damage [34]. Synaptic repair can occur in 5 days [35], but most hair cell damage remains which is probably responsible for the long-term threshold shifts. It has also been demonstrated that dendrite damage could be prevented by perfusing a glutamate antagonist [35], or a dopaminergic agonist [34], into the cochlea during the noise exposure. However, it is essential to find *curative* drugs to treat patients who underwent acoustic trauma and to address both the hair cell injuries and the dendrite damage.

3. Experiment

The actual efficiency of the classical medical treatments of the acoustic trauma was assessed by using a well-standardized animal study by d'Aldin et al. [36]. The results are related to the effect of the most widely used medical treatments. The effects of acoustic trauma are evaluated by electrocochleography (Compound Action Potentials : CAP), and by observation of the anatomical alterations of the outer and inner hair cells (Scanning Electron Microscopy : SEM).

Pigmented guinea pigs are exposed to one-third octave band noise centered on 8 kHz at 129 dB SPL during 20 minutes. Continuous noise is used despite the fact that impulse noises represent the biggest hazard in the military environment because interindividual variability is smaller following exposure to continuous noise (up to now, in that study only a few animals have been exposed to impulse noises). Post-exposure audiograms (from 2 to 32 kHz) are performed 20 minutes and 1,2,3,7 and 14 days later and compared to the pre-exposure audiogram. After the last audiogram, the cochleas are prepared for SEM. The organ of Corti is thoroughly analyzed with respect to damage to inner and outer hair cells. Stereocilia pathology is defined according to Borg [37] : destroyed (a total loss of the stereocilia bundle), damaged (more than 10% disarray, fallen or lost stereocilia). Data are plotted as cochleograms representing the percentage of intact, damaged and destroyed hair cells every 200 microns from 2 to 10 mm from the base (first and then a half turn).

For each group of animals (n = 10), the treatment begins 1 hour after the end of the sound exposure and lasts for 5 days.

Carbogen therapy : carbogen mixture (7% carbon dioxide and 93% oxygen) is delivered at ambient

Hyperbaric oxygen therapy : animals are placed inside a pressure chamber. The chamber is pressurized at 2.5 ATA with 100% oxygen. The pressure is then held for 1 hour, twice a day. Decompression lasts 10 minutes.
Corticoid therapy : methylprednisolone hemisuccinate 2, 20, 40 or 100 mg/kg is given once a day by IM injection.
Combined hyperbaric oxygen – corticoid therapy : animals receive corticoids (20 mg/kg) and breathe hyperbaric oxygen (2.5 ATA).

4. Results

Figure 1 represents the results obtained in control (untreated) animals (n = 10). On the fourteenth day, the largest threshold elevation (about 20 dB) is observed between 8 and 13.4 kHz.

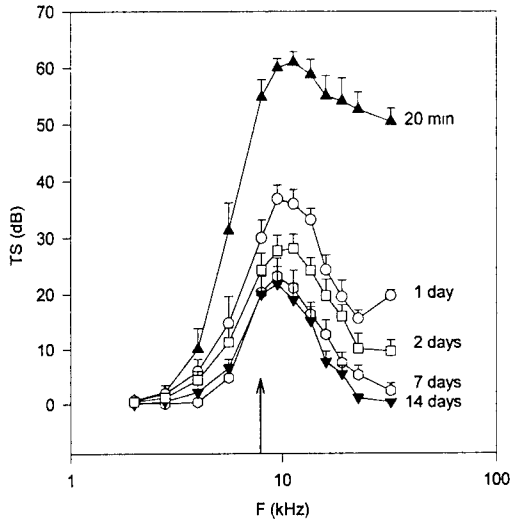

Figure 1 : CAP threshold shifts in dB
(mean value + 1 standard deviation)
(arrow shows exposure frequency)

To compare the threshold shifts (TS) and the cochlear damage, the audiograms and the cochleograms are scaled to adjust the distance from the base of the cochlea to the frequency. Three individual examples are given. The first example (figure 2) shows significant TS and cochlear damage (particularly in the first row of outer hair cells. The second example (figure 3) shows no TS (complete recovery) and no morphological damage. The third example (figure 4) shows that despite complete TS recovery, significant morphological damage can be observed. This indicates that CAP audiograms are not enough to fully assess a complete recovery (functional and morphological). Therefore, in man, an apparently complete functional recovery, as assessed by behavioral audiometry, does not exclude the possibility of (limited) hair cell damage. Such damage could make subjects more sensitive in case of further noise exposures and more susceptible to presbyacousis. Therefore, complementary functional tests (i.e., distortion product recordings which address directly the OHC) are advised.

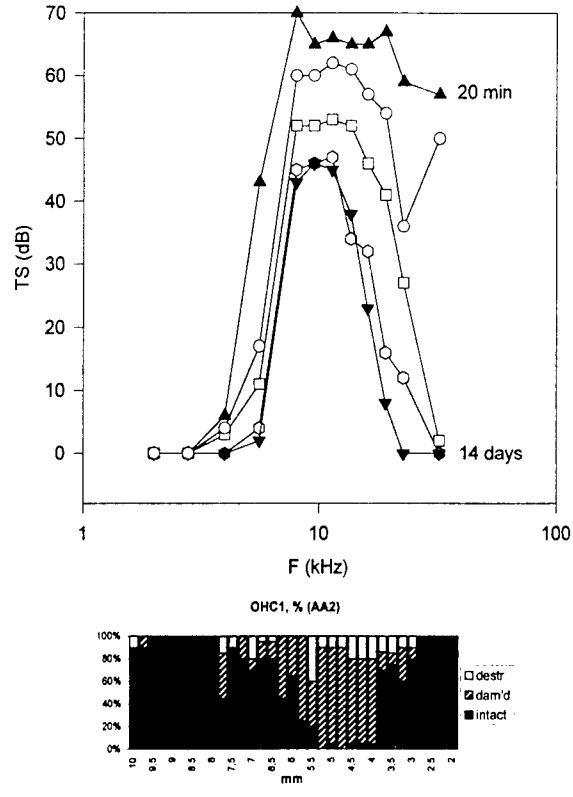

Figure 2 : TS and damage to the first row of OHC in a control animal

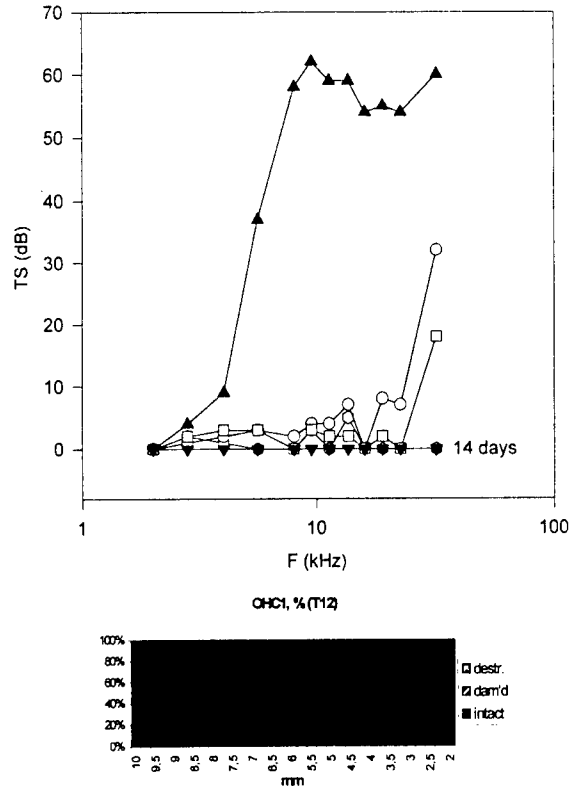

Figure 3 : TS and damage to the first row of OHC in a control animal

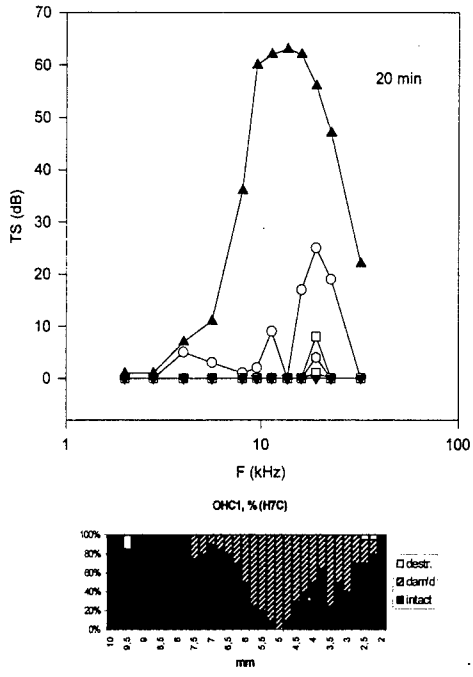

Figure 4 : TS and damage to the first row of OHC in a control animal

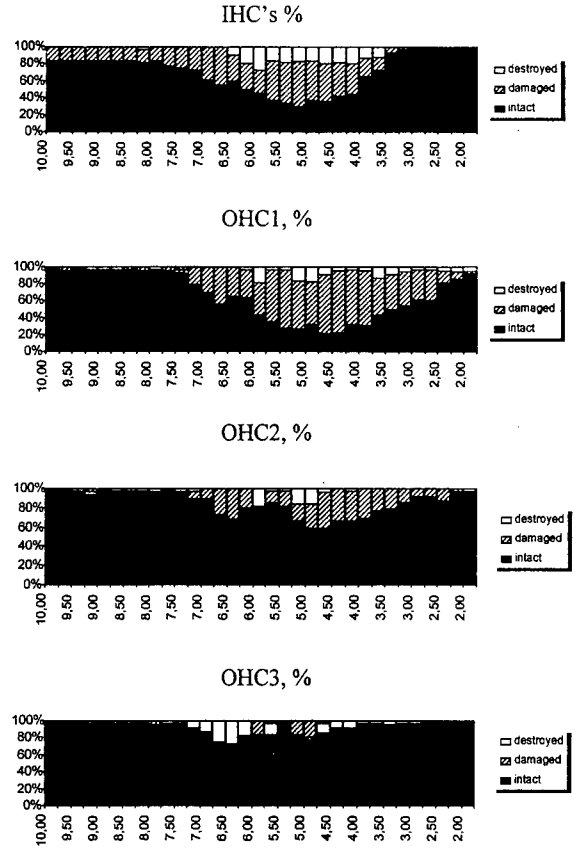

Figure 5 : Cochlear damage observed 14 days after acoustic trauma in controls (mean of 10 animals)

Figure 5 shows the cochlear damage observed 14 days after the acoustic trauma in control animals. The stereocilia of the first OHC row are the most sensitive.

Carbogen therapy : no significant difference for audiograms can be observed between the controls and carbogen-treated animals 14 days after acoustic trauma (figure 6). The cochlear damage (mean cochleogram) is not significantly different of that observed in controls (figure 5).

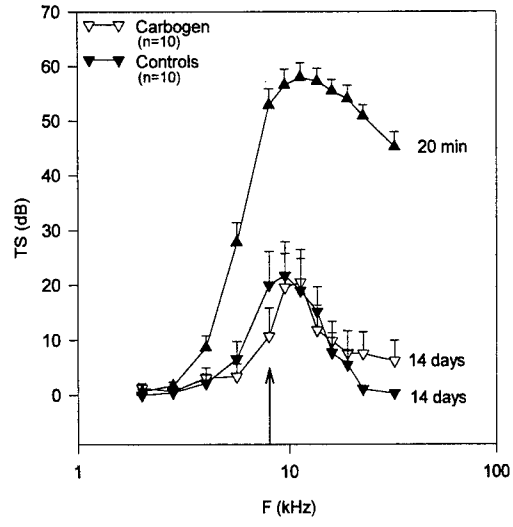

Figure 6 : TS in dB (mean + 1 standard deviation) observed 14 days after the acoustic trauma in controls and carbogen-treated animals

Oxygen therapy (ambient pressure) : as for the carbogen therapy, no significant difference is observed between controls and treated animals 14 days after acoustic trauma either for audiograms or for cochleograms.

Hyperbaric oxygen therapy : TS at day 14 are higher (40 dB instead of 20 dB) (figure 7) and cochlear damage is greater than in the control group (figure 8).

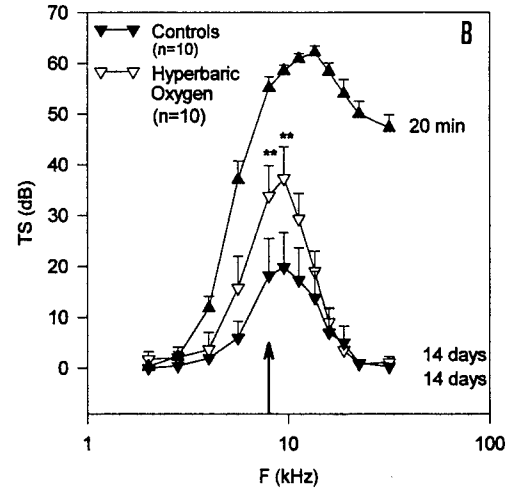

Figure 7 : TS observed at day 14 in controls and hyperbaric oxygen treated animals (** : $0.001<p<0.01$)

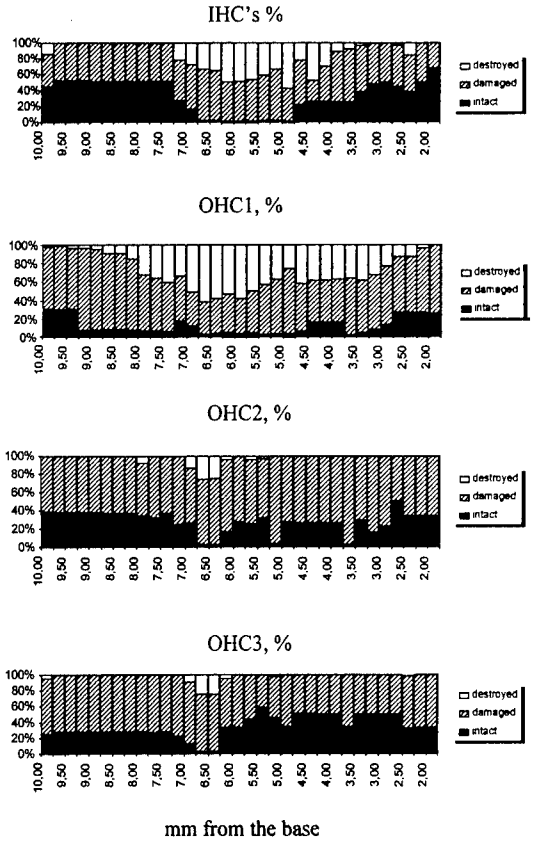

Figure 8 : Cochlear damage observed 14 days after acoustic trauma in hyperbaric oxygen treated animals (mean of 5 animals)

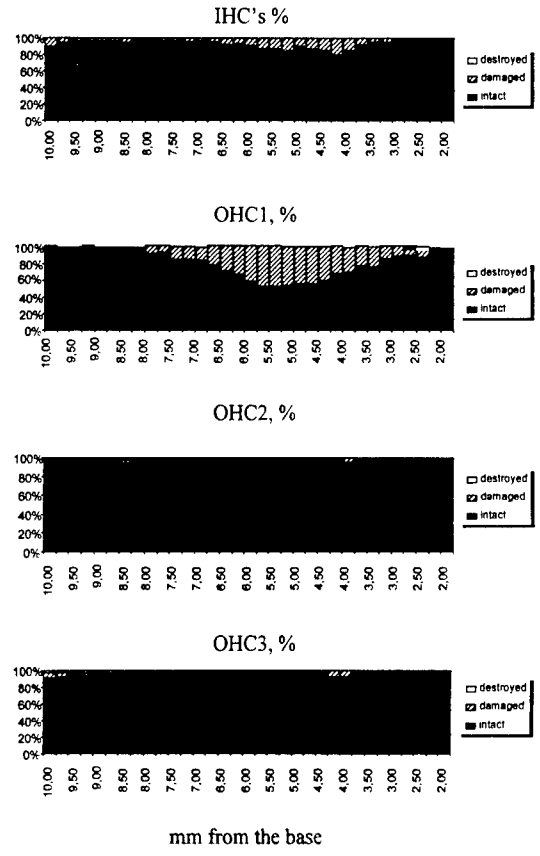

Figure 10 : Cochlear damage observed 14 days after acoustic trauma in corticoid treated animals (20 mg/kg) (mean of 10 animals)

Corticoid therapy : when the animals are treated once a day (for 5 days) with corticoid doses of 20 mg/kg, the TS recovery is faster and is improved : TS at day 14 are smaller (10 dB instead of 20 dB) (figure 9). Moreover, the cochlear damage observed on the fourteenth day in the treated animals is much smaller than in the controls and is almost restricted to the first OHC row (figure 10).

Dose-Dependent effect of corticoid : similar results are obtained when the corticoid dose is 10 mg/kg (doses larger than 20 mg show no further improvement either of the TS recovery or of the cochlear damage, doses smaller than 10 mg look ineffective).

Influence of the delay of the corticoid treatment : usually, the soldiers suffering acute acoustic trauma cannot be treated as early as one hour after the exposure.

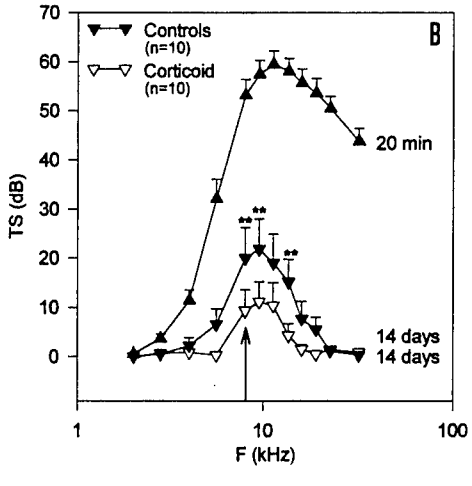

Figure 9 : TS observed at day 14 in controls and corticoid treated animals (20 mg/kg) (**: 0.001<p<0.01)

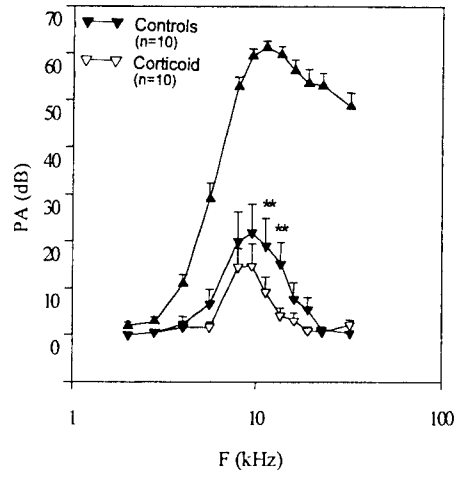

Figure 11 : TS observed at day 14 in controls and corticoid treated animals (20 mg/kg, first injection : 24 hours post exposure)

Therefore, another group of animals (n = 10) received the first injection of corticoids (20 mg/kg) 24 hours after the acoustic trauma (instead of 1 hour). The results which have been obtained are very similar to the previous experiment (figures 11 and 12).

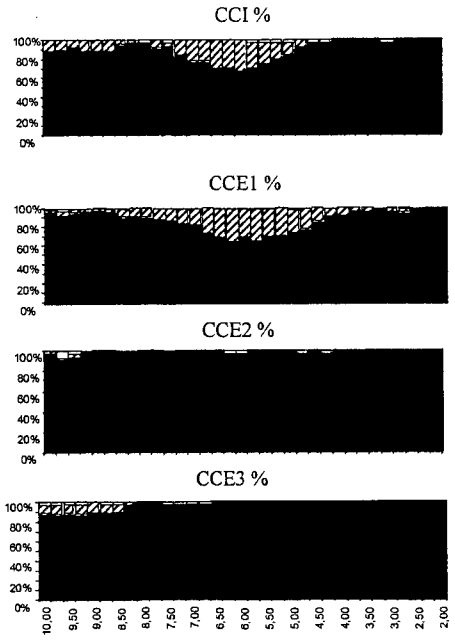

Figure 12 : Cochlear damage observed 14 days after acoustic trauma in corticoid treated animals (20 mg/kg, first injection : 24 hours post exposure) (mean of 10 animals)

The corticoid therapy is effective even when the delay of the treatment is 24 hours post exposure.

Combined hyperbaric oxygen – corticoid therapy: combining these therapies significantly improved the functional and morphological recovery (figure 13).

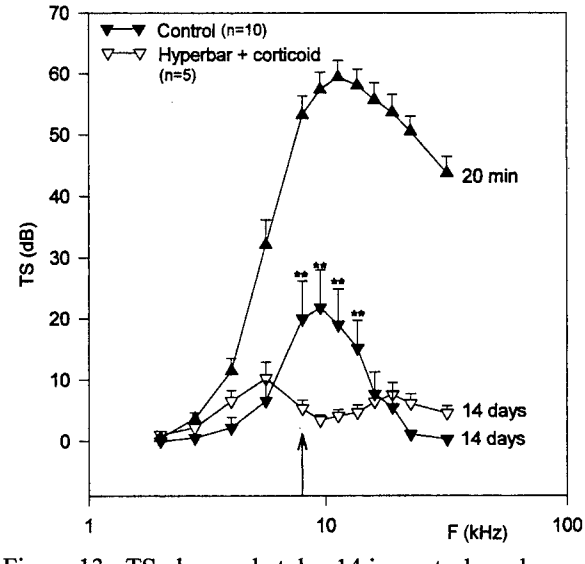

Figure 13 : TS observed at day 14 in controls and combined corticoid (20 mg/kg, first injection : 1 hour post exposure) - hyperbaric oxygen treated animals (n = 5) (**: 0.001<p<0.01)

These results are confirmed by a study of Lamm and Arnold [38] who observed that the combination therapy of hyperbaric oxygen and prednisolone achieved the best results of all treatments tested during acute experiments (3 hours post-exposure) performed on guinea pigs.

Corticoid therapy combined with hyperbaric oxygen therapy seems to help the hair cells to recover after an acute acoustic trauma. Without treatment, the hair cell damage remains stable or worsens between the immediate post-exposure period and day 14 (figures 13 and 14).

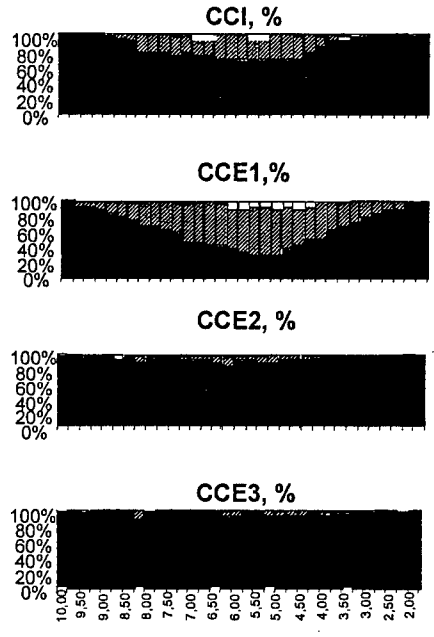

Figure 13 : Cochlear damage observed 1 hour after acoustic trauma in control animals (n = 10)

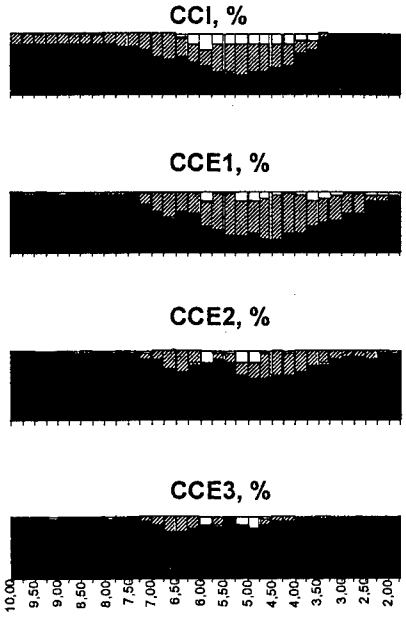

Figure 14 : Cochlear damage observed 14 days after acoustic trauma in control animals (n = 10)

Acoustic trauma from impulse noise

Acute acoustic trauma occurring in the military are mostly due to impulse noise. For impulse noise, it is very likely that the mechanical damage is the first and the main reason for NIHL. Therefore, it is also necessary to study the efficiency of the medical treatments following impulse noise exposures.

Guinea pigs have been exposed to impulse noises produced by primers. Number of rounds was 20 or 30 with 5 seconds intervals. The peak pressure level at the pinna ranged from 1 to 2.5 KPa corresponding to 154 to 162 dB peak (duration of the first positive phase: 0.12 ms). A control group was compared to a treated group with intra-muscular injection of methylprednisolone at the rate of 20 mg/kg; 1 hour after the trauma and once a day during 6 days after exposure.

The first results confirm the very large interindividual variability of the NIHL due to impulse noise and the "critical level" concept [38,39]. Control animals were exposed to 20 rounds of 2KPa peak pressure. Some animals present a very good recovery and almost no cochlear damage, some others present large TS at 14 days and complete destruction of OHC and IHC. Treated animals seem to recover better [40]. However, many more animals are still to be exposed and treated to know whether the treatment is efficient or not.

5. Discussion

Blood Flow Promoting Therapy

According to Lamm and Arnold [41], the cochlear hypoxia occurs simultaneously with hearing loss after exposure to impulse noise, gun shots, and broadband noise. Conventional approach to treating tissue ischemia and hypoxia is the administration of blood-flow-promoting drugs which affect vascular diameter, vascular permeability, membrane flexibility of red blood cells, blood osmolarity, plasma volume, and plasma viscosity, thereby improving microcirculation and tissue oxygenation.

One of these agents is the hydrophilic osmotic compound hydroxyethyl starch (HES), which is known to increase plasma volume, thereby decreasing plasma viscosity. As observed by Lamm and Arnold, in the noise-damaged ischemic cochlea the blood-flow-promoting effect is more pronounced and lasts longer after infusion of the high molecular HES 200 (compared to the low molecular HES 70). Since hemodilution due to the increase in plasma volume is more pronounced during HES 200, polarographic registration of PO2 does not improve. In contrast the less hemodilutive effect of the low molecular plasma expander induces a significant improvement of PO2, although full compensation of noise-induced cochlear hypoxia is not achieved. As compensation of noise-induced cochlear ischemia, the improvement of PL-PO2 ceases after termination of the infusion due to the relatively short plasma expansive effect of HES 70. However, both drugs show similar effects on auditory evoked potentials. Cochlear microphonic potential (CM) is partially restored and compound action potential (CAP) and auditory brain stem response (ABR) fully recover. It is assumed, that the osmotic effect of these hydrophilic compounds may contribute to restoration of disturbed cellular osmolarity and thereby cellular function. This hypothesis is supported by the observation that the vasodilator pentoxifylline (which has no such osmotic effect), fully compensated noise-induced cochlear ischemia and hypoxia, but had no therapeutic effect on NIHL (Lamm and Arnold) [41]. Simultaneous infusion of pentoxifylline and HES 70 or HES 200 does not attain better results than the monotherapy with HES 70 or HES 200.

Ginkgo biloba and naftidrofuryl are supposed to improve microcirculation, and thereby tissue oxygenation due to various effects not clarified so far. In the noise-damaged cochlea, however, blood flow and PO2 are temporarily improved during ginkgo infusion, but do not change with naftidrofuryl. As observed after infusion of isotonic saline (placebo), noise-induced reduction of CM, CAP, and ABR amplitudes do not differ from the untreated group, indicating that ginkgo biloba and naftidrofuryl had no therapeutic effect.

Carbogen is considered one of the most powerful vasodilators of cerebral capillary beds, and many studies indicate that carbogen inhalation during exposure to noise results in a significant reduction in noise-induced hearing losses [42]. Brown et al. [43] also found significantly less outer hair cell loss in guinea pigs given carbogen during a 120-dB broad-band noise exposure compared to a control group. It is assumed that the C02, in carbogen acts synergistically with oxygen in carbogen to produce increased oxygenation of cochlear tissues and to reduce cochlear damage. However, as previously reported by Hatch et al. [44], d'Aldin et al. [36] observed no significant difference between the carbogen-treated animals after the noise exposure and the control group. Therefore, carbogen could have a protective effect, but with much less curative efficiency.

Isobaric Oxygen Therapy

The idea that inhalation of pure oxygen could be used as a medical treatment for acoustic trauma is based on experimental studies which have shown that high-intensity noise causes cochlear hypoxia, which correlates with post-exposure hearing loss (Lamm and Arnold) [45]. These authors reported that cochlear hypoxia reflects an increased extraction rate from cochlear fluids. In another study, however, they showed that noise-induced cochlear hypoxia is not compensated by oxygen delivered at an ambient pressure level [46]. Improvement in threshold shifts is reported only when pure oxygen is given during noise exposure [44]. Accordingly, the effectiveness of oxygen delivered at the ambient pressure level after intense noise exposure is not shown in the study of d'Aldin et al. [36].

Hyperbaric Oxygen Therapy

The aim of hyperbaric oxygen (HBO) administration is to significantly improve partial oxygen pressure in

inhaled air. Oxygen is diffused from the various terminal cochlear capillary networks into the perilymph and cortilymph, supplying the sensory and peripheral neuronal structures of the inner ear, since these are not directly vascularly supplied. These diffusion paths are extremely long com-pared with noncochlear tissues. In this respect, the PO2 in the perilymph and cortilymph will only show a constant rise after an extreme increase in the arterial PO2 and thereby of the arterial-perilymphatic difference in oxygen concentration. This can only be achieved with HBO (with isobaric oxygenation, this difference in oxygen concentration is not high enough to show a clear and constant increase in intracochlear). The oxygen-induced reduction in cochlear blood flow in the noise-exposed ischemic cochlea is more pronounced after hyperbaric oxygenation compared to isobaric oxygenation. However, sixty minutes after termination of HBO, the cochlear blood flow is not significantly worse than in the untreated group Sustained compensation of noise-induced cochlear hypoxia is achieved most effectively by HBO. However, Lamm and Arnold [41] observed that an improvement in cochlear blood flow is not necessarily associated with improvement of auditory function..

At 2 ATA hyperbaric oxygen, the amount of oxygen and blood-dissolved oxygen fraction available are multiplied by 10. In the study of d'Aldin et al. [36], no improvement in threshold shifts can be observed, however, under those hyperbaric conditions. On the contrary, either at 2.5 or 1.5 ATA, hyperbaric oxygen treatment results in a higher threshold shift and additional hair cell damage.

Thus, oxygen administration is not decisive for medical treatment of acoustic trauma. Moreover, the higher threshold shift and additional hair cell damage observed in the d'Aldin's study, together with the fact that this treatment induces barotrauma in up to 50% of the human patients, suggest that hyperbaric oxygen should not be used –alone - as an acute treatment.

Antiphlogistic Therapy

According to Lamm and Arnold [41], the rationale for administration of anti-inflammatory agents in noise-induced cochlear alterations is based on the observation that inflammatory tissue alterations are not only elicited by bacterial, viral, or other immunopathological processes, but also by physically induced cellular damage, tissue hypoxia, and tissue ischemia [47].

In non-cochlear mechanically induced and/or hypoxic tissue an abnormal histamine liberation and/or release of eicosanoids such as prostaglandine, prostacyclin, thromboxanes, and leucotriens has been observed [47]. This results in various vascular effects, such as local arteriolar and capillary dilation and/or constriction and increased vascular permeability, all of which were also observed in sections of noise-damaged cochlear tissue. In this respect, an abnormal liberation of histamine and/or eicosanoids may be involved in the development of progressive cochlear ischemia beginning 30 min after termination of noise. It is assumed therefore, that anti-inflammatory drugs such as histamine H1-receptor antagonist, diclofenac sodium, and the synthetic glucocorticoid prednisolone (which counteract abnormal histamine liberation and/or release of eicosanoids), can relieve posttraumatic cochlear ischemia and the progression of noise-induced cochlear hypoxia. However, this is not the case at all.

In a recent study, Lamm and Arnold showed that prednisolone induces a significant decay in partial oxygen pressure in the perilymph as well in animals unexposed as in animals exposed to noise. These results indicate that corticoid induces oxygen consumption. In the short term (up to 3 hours post-exposure) study of Lamm and Arnold [41], there were no significant differences in the values for cochlear blood flow between the noise-exposed untreated group, the placebo-treated group and the groups treated with histamine N1-receptor antagonists diclofenac sodium, and prednisolone, administered either at a low or high dose. However, even though none of the applied drugs relieved progressive noise-induced cochlear hypoxia and post-traumatic ischemia, it is interesting to note that diclofenac induced partial restoration of CM and CAP amplitudes and full restoration of ABR. Following a high dose of prednisolone, there was again only a partial recovery of CM, but full restoration of CAP and ABR. A low prednisolone dose affected CAP only, while the histamine H1-receptor antagonist and isotonic saline had no therapeutic effect [41].

These findings indicate direct cellular effects of diclofenac and prednisolone in the cochlea. However, the precise mechanisms involved is mere speculation. Some of the cellular effects may contribute to related intracochlear early recovery processes associated with restoration of auditory function. In addition, prednisolone binds with equal affinity to both glucocorticoid and mineralo-corticoid receptors, the latter of which is very evident in peripheral auditory nerves and spiral ganglion cells. Binding by mineralocorticoid receptors results (among other effects) in an activation of the enzyme sodium-potassium-ATPase, which may contribute to restoration of disturbed cellular osmolarity, electro-chemical gradients, and neuronal conduction. At this point we have to remind that d'Aldin et al. [34] and Puel et al. [35] demonstrated that dendritic damage at the base of inner hair cells, the latter representing the site of CAP generation, accounts for half the contribution to acute hearing loss after acoustic trauma (especially in case of continuous noise exposure).

In the long term study of d'Aldin et al. [36], when the first injection of corticoid is given 1 h or 24 hours after exposure to noise, noise-induced threshold shift is decreased, recovery is faster, and less hair cell damage is observed (noise-induced hearing loss observed one day after corticoid administration: 25 dB, is almost equivalent to that observed 14 days after exposure in untreated animals: 20 dB). Thus, it seems that corticoid acts both at the dendritic and the cellular level. D'Aldin

et al. agree with the hypothesis of Lamm and Arnold: the activation of the enzyme Na, K-ATPase by corticoid may contribute to the restoration of disturbed cellular osmolarity, electrochemical gradients, and neuronal conduction. (indeed this enzyme is widely distributed in the cochlea, including the base of the outer and inner hair cells).

Even though the exact mechanism by which corticoids influence the inner ear function in those studies remains speculative, corticoid should be prescribed in treatment of acoustic trauma.

Combined Hyperbaric Oxygen-Corticoid Therapy

Corticoids induce oxygen consumption in order to mobilize amino acid for glucogenesis and to alter glucose utilization by oxygen-consuming mechanisms [48]. This oxygen consumption could explain the decline of partial oxygen pressure in the perilymph, observed in animals exposed to sound and treated by corticoids by Lamm and Arnold [47]. Moreover, acoustic overstimulation induces cochlear hypoxia which occurs simultaneously with hearing loss (this hypoxia reflects an increased oxygen consumption and hence increased extraction from cochlear fluids).

Thus, it looks interesting to combine corticoid and hyperbaric oxygen treatment. Improving partial oxygen pressure in inhaled air could compensate for the decline in partial oxygen pressure and thus potentiate corticoid effect. In agreement with this hypothesis, the results of d'Aldin et al. [36] indicate that combined corticoid and hyperbaric therapies significantly improve functional and, in a very striking way, morphological recovery. These results are in accord with those reported by Lamm et al., [41,47] in which hyperbaric oxygen combined with prednisolone gave best results.

These findings indicate first that effective treatment modalities of acute noise-induced hearing loss are available, and second that the therapeutic effects are not directly associated with blood-flow promotion and re-oxygenation, but involve other effects on the cellular level.

6. Perspective

A lot remains to be done to investigate the interest of other drugs (magnesium [49]...), the influence of the delay of implementation of the treatments and, most of all, to assess the actual efficiency of the treatments of the acute acoustic trauma following the exposure to impulse noise.

Moreover, experiments are in progress:

- to assess the interest of local treatments (i.e., the medicaments are applied directly to the inner ear [50]) which could be used together with the systemic treatments (i.e., the medicaments are given by perfusion to the whole body), or alone,
- to evaluate the interest of new treatments [51,52,53] which take advantage of the last advances in molecular biology (anti-oxydants, neurotransmitters agonists or antagonists, growth factors...) and could, besides cell preservation [54] and NIHL better recovery, lead to a decrease of the annoyance due to noise exposure related effects like tinnitus.

The increasing knowledge of molecular mechanisms, together with the development of new experimental approaches, is very promising for future clinical applications. Future progress will require that a method be developed and validated for the local application of drugs directly into the cochlea of human subjects.

REFERENCES

1. Ward, W.D., "The concept of susceptibility", J. Occup. Med. 7, 1965, 595
2. Howell, K., "Susceptibility to Noise-Induced Hearing Loss", I.S.V.R., Contract Rept. N°82/20, London, 1982
3. Buck, K. and Franke, R., "Can TTS be an indicator for individual susceptibility to PTS?", in "Basic and Applied Aspects of Noise-Induced Hearing Loss", Salvi R.J. et al., Eds., NATO ASI Series A: Life Sciences, 111, 1986, 441
4. Bonaccorsi, P., "U colore dell'iride cone "test" di Valutazione quantitativa, nell'nemo della concentratione di melamina nella striavasculare", Annali Lar. Otol. Rhinol. Fraing., 64, 1965, 725
5. Jansen, G., "Relation between temporary threshold shift and peripheral circulatory effects of sound", in "Physiological Effects of Noise", Welch and Welch Eds., 1970, Plenum, New York
6. Rosen, S., Plester, D., El-Mofty, A. and Rosen, H.V., "Relation of hearing loss to cardiovascular disease", Trans. Am. Acad. Ophtalmo. Otolaryngol. 68, 1964, 433
7. Carhart, R.H., "Updating special hearing tests in otological diagnosis", Arch. Otolaryngol., 97, 1973, 88
8. Humes, L.E., Schwartz, D.M. and Bess, F.H., "The threshold of octave masking (TOM) as a predictor of susceptibility to noise-induced hearing loss", J. Audit. Res., 17, 1977, 5
9. Bienvenue, G.R., Violin-Singer, J.R. and Michael, P.L., "Loudness discrimination index (LDI): a test for early detection of noise susceptible individuals", Am. Ind. Hyg. Assoc. J., 38, 1977, 333
10. Pederson, C.B., "Brief tone audiometrie in patients with acoustic trauma", Acta Otolaryngol. (Stockholm), 75, 1973, 332
11. Pederson, C.B., "Brief tone audiometrie", Scand. Audiol., 5, 1976, 27
12. Humes, L.E., "Review of four new indices of Susceptibility to Noise-Induced-Hearing-Loss", J. Occup. Med., 19, 1977, 116
13. Botte, M-C., Baruch C. and Dancer, A., "TTS as a function of exposure frequency", J. Acoustique, 3, 1990, 53
14. Dancer, A., "Use of animal models in the study of the effects of noise on hearing", in "Occupational

Medicine: State of the Art Reviews", Hanley and Belfus Eds., Philadelphia, 10, 1995, 535
15. Hohansson, B., Kylin, B. and Langfy, M., "Acoustic reflex as a test of individual susceptibility to noise", Acta Otolaryngol., 64, 1967, 256
16. Puel, J.L. and Vassout, P., "Medial efferents and acoustic trauma", in "Noise-Induced Hearing Loss", Dancer A. et al. Eds., Mosby Year Book, 1992, 415
17. Rajan, R., "Protective functions of the efferent pathways to the mammalian cochlea: a review", in "Noise-Induced Hearing Loss", Dancer A. et al. Eds., Mosby Year Book, 1992, 429
18. Liberman Ch., "Does olivocochlear feedback protect the cat's inner ear from acoustic injury", in "Noise-Induced Hearing Loss", Dancer A. et al. Eds., Mosby Year Book, 1992, 423
19. Temkin, J., "Die Schädigung des Ohres durch Lärm und Erschütterung", Mschr. Ohrenheilk. und Laryngo-Rhinologie, 67, 1993
20. Burns, W. and Robinson, D.W., "Hearing and Noise in Industry", HMSO, 1970, London
21. Richartz, G., "Untersuchungen zur individuellen Lärmempfindlichkeit beim Menschen", PhD, Technische Univ. Dresden, 1976
22. Kraak, W., "Integration of TTS for permanent threshold shift", in "Noise as a Public Health Problem", Am. Speech and Hearing Associated Report n° 10, 1980
23. Kraak, W., "Investigations on criteria for the risk of hearing loss due to noise", in "Hearing Research and Theory", Tobias J.V. and Schubert E.D. Eds., Academic Press, 1, 1981, New York
24. Kryter, K.D., Ward, W.D., Miller, J.D. and Eldredge D.H., "Hazardous exposure to intermittent and steady-state noise", J. Acoust. Soc. Am., 39, 1966, 451
25. Jerger, J.F. and Carhart, R., "Temporary threshold shift as an index of noise susceptibility", J. Acoust. Soc. Am., 28, 1956, 611
26. Pfander, F., "Höhe der temporären Schwellen-abwanderung (TTS) in Audiogramm und Rückwanderungszeit geräusch und knallbelasteter Ohren als Test knallgefärdeter Hörorgan", Arch. Ohr.-Nas.-u.Kehlk.-Heilk., 191, 1968, 586
27. Job, A., Raynal, M. and Rondet, Ph., "Hearing loss and use of personal stereos in young adults with antecedents of otitis media", The Lancet, 353, 1999, 35
28. Probst, R., "Clinical treatment of acoustic trauma", French-German Research Institute of Saint-Louis, France, 1998
29. Ohlin, D., "Cost Effectiveness of Hearing Conservation Programs", ibidem
30. Saunders, J.C., Dear, S.P. and Schneider, M.E., "The anatomical consequences of acoustic injury: a review and tutorial", J. Acoust. Soc. Am., 78, 1985, 833
31. Spoendlin, H., "Primary structural changes in the organ of Corti after acoustic overstimulation", Acta Oto-Laryngol., 71, 1971, 166
32. Robertson, D., "Functional significance of dendrite swelling after loud sounds in the guinea pig cochlea", Hear. Res., 9, 1983, 263
33. Pujol, R., "Sensitive developmental period and acoustic trauma: facts and hypotheses", in "Noise-Induced Hearing Loss", Dancer A. et al. Eds., Mosby Year Book, 1992, 196
34. d'Aldin, Ch., Puel, J-L., Leducq, R., Crambes, O., Eybalin, M. and Pujol, R., "Effects of a dopaminergic agonist in the guinea pig cochlea", Hear. Res., 90, 1995, 202
35. Puel, J-L. et al., "Protective effect of glutamate antagonist kynurenate on noise-induced hearing loss", in "Advances in Noise Research: Biological Effects of Noise", Prasher, D. and Luxon, L., Eds., Whurr London, 1, 1998, 261
36. d'Aldin, Ch., Cherny, L., Devrière, F. and Dancer, A., "Treatment of acoustic trauma", in "Ototoxicity" Henderson et al., Eds., Annals of the New York Acad. of Sc. 884, 1999, 328
37. Borg, E., Canlon, B. and Engstrom, B., "Noise-induced hearing loss", Scand. Audiol., Suppl. 40, 1995, 1
38. Kryter, K.D. and Garinther, G., "Auditory effects of acoustic impulses from firearms", Acta-Otolaryngol., Suppl. 211, 1966
39. Price, G.R., "Mechanisms of loss for intense sound exposures", in "Hearing and other Senses", Fay and Goweritch Eds., Amphora Press, 1983
40. Magnan, P., d'Aldin, Ch. And Dancer, A., "Efficiency of a medical treatment of the acoustic trauma following impulse noise exposure in the guinea pig", J. Acoust. Soc. Am., 105, 1999, 1296
41. Lamm, K. and Arnold, W., "Successful treatment of Noise-Induced Cochlear Ischemia, Hypoxia, and Hearing Loss", in "Ototoxicity" Henderson et al., Eds., Annals of the New York Acad. of Sc. 884, 1999, 233
42. Witter, H.L., Deka, R.C., Lipscomb, D.M. and Shambaugh, G.E., "Effects of prestimulatory carbogen inhalation on noise induced temporary threshold shifts in humans and chinchillas", Am. J. Otol., 1, 1980, 227
43. Brown, J.J., Meikle, M.B. and Lee, C.A., "Reduction of acoustically induced auditory impairment by inhalation of carbogen gas (temporary pure tone induced depression of cochlear action potentials)", Acta Otolaryngol., 100, 1985, 218
44. Hatch, M., Tsai, M., Larouere, M.J., Nuttall, A.L. and Miller, J.M., "The effects of carbogen, carbogen dioxide, and oxygen on noise-induced hearing loss", Hear. Res., 56, 1991, 265
45. Lamm, K. and Arnold, W., "Noise-induced cochlear hypoxia is intensity dependent, correlates with hearing loss, and precedes reduction of cochlear blood flow", Audiol. Neurootol., 1, 1996, 148
46. Lamm., K., Lamm, C. and Arnold, W., "Effect of isobaric oxygen versus hyperbaric oxygen on the

normal and noise-damaged hypoxic and ischemic guinea pig inner ear", Adv. Otorhinolaryngol., 54, 1998, 59

47. Lamm, K. and Arnold, W., "The effect of prednisolone and non-steroidal anti-inflammatory agents on the normal and noise-damaged guinea pig inner ear", Hear. Res., 115, 1998, 149
48. McMahon, M., Gerich, J. and Rizza, R., "Effects of glucocorticoids on carbohydrate metabolism", Diabetes Metab. Rev., 4, 1988, 17
49. Attias, J. and Bresloff, I., "Oral magnesium reduces noise induced temporary and permanent hearing loss", in "Cochlear Pharmacology and Noise Trauma", Prasher, D. and Canlon, B., Eds., Noise Research Network Publications, London, 1999, 43
50. Dauman, R., "Preliminary thoughts on the type of patients who could benefit from in situ pharmacology", in "Cochlear Pharmacology and Noise Trauma", Prasher, D. and Canlon, B., Eds., Noise Research Network Publications, London, 1999, 191
51. Sjaak, F., Klis, L., Frank, P., Hamers, T., John, C.M., De Groot, J. and Smoorenburg, G. "Protection against cisplatin ototoxicity by melanocortins", in "Cochlear Pharmacology and Noise Trauma", Prasher, D. and Canlon, B., Eds., Noise Research Network Publications, London, 1999, 181
52. Puel, J-L., d'Aldin, Ch., Ruel, J., Ladrech, S. and Pujol, R., "Perspectives in inner ear pharmacology and clinical appplications", in "Cochlear Pharmacology and Noise Trauma", Prasher, D. and Canlon, B., Eds., Noise Research Network Publications, London, 1999, 1
53. Henderson, D., McFadden, S.L., Xiang Yang Zheng, Kopke R. and Hight, N., "Intervention possibilities for noise induced hearing loss", in "Cochlear Pharmacology and Noise Trauma", Prasher, D. and Canlon, B., Eds., Noise Research Network Publications, London, 1999, 85
54. Waters, C., "Molecular mechanisms of cell death in the ear", in "Ototoxicity" Henderson et al., Eds., Annals of the New York Acad. of Sc. 884, 1999, 41